Commentary on "Brain Environment Interactions: Stress, Posttraumatic Stress Disorder, and the Need for a Postmortem Brain Collection"

What's Missing in Posttraumatic Stress Disorder Research? Studies of Human Postmortem Tissue

John H. Krystal and Ronald Duman

The interplay of genes and environments is highlighted by posttraumatic stress disorder (PTSD). The field of PTSD research has struggled to define the type of stressors that distinguish "ordinary" stress from "traumatic" stress (Breslau and Kessler, 2001). Similarly, this field of research has long considered the importance of genetic (Krystal et al., 1998; Segman et al., 2002) and environmental factors that predispose or protect (Stein et al., 2002) individuals from traumatization, that is, when many people are exposed to the same stress, why do only a few people develop PTSD?

As thoughtfully reviewed by Osuch and her colleagues in this issue, within the field of PTSD research, the principal epigenetic question at the moment is whether stress damages the brain. There is no real debate as to whether this is a possibility (Bremner, 1999). An elegant body of preclinical research indicates that under certain circumstances glucocorticoids and glutamate interact to damage or kill neurons in the CA3 region of the hippocampus and perhaps other brain regions (McEwen, 2000; Sapolsky, 2000). More recently, other destructive effects of stress have been identified including atrophy (Magarinos, Verdugo, and McEwen, 1997), programmed cell death (apoptosis) (Lucassen et al., 2001), and depletion of neuronal populations due to disruption of the proliferation of new nerve cells (neurogenesis) (Gould et al., 2000). In parallel, there is emerging evidence that pharmacologic treatments for mood disorders and PTSD appear to protect against or reverse these effects of stress exposure (Duman, Malberg, and Thome, 1999). The disruption of neurogenesis by stress and the reversal of this process by antidepressant treatment is illustrated in Figure 1.

The clinical evidence that stress damages the brain came from a series of magnetic resonance imaging (MRI) studies that indicated that the volume of hippocampus was re-

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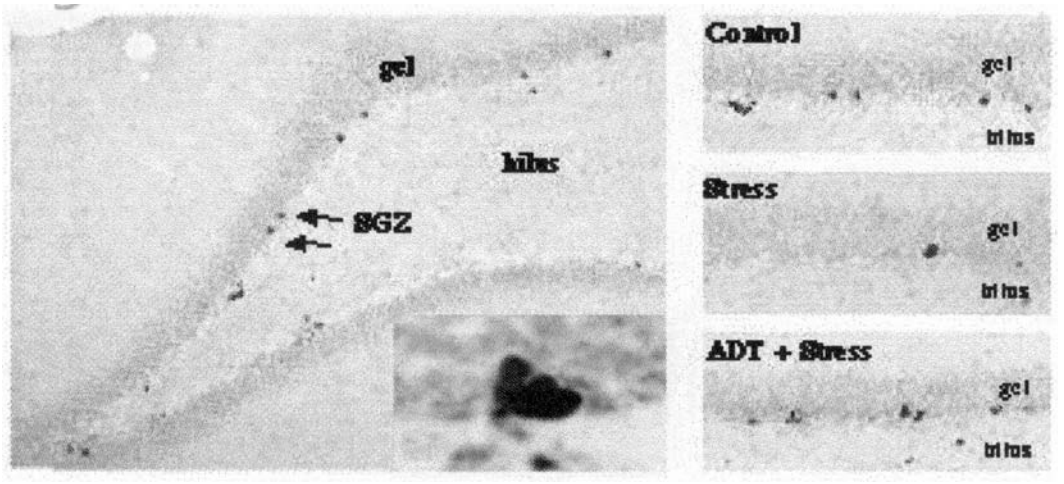

Figure 1.
Stress and Antidepressant Effects on Neurogenesis in the Adult Hippocampus. In these figures, "new" neurons appear black because they have taken up bromodeoxyuridine (BrdU). Figure 1A (left side): the formation of new cells is illustrated in a healthy hippocampus in the deep layers of the hippocampus where stem cells differentiate into new neurons. The insert shows a new neuron at higher field. Figure 1B (upper right side) presents a typical rate of neurogenesis in a reference region of the hippocampus. Figure 1C (middle right side) depicts a reduction of the number of BrdU-stained neurons in a stressed adult rat, reflecting a reduction in neurogenesis. In Figure 1D (bottom right side), antidepressant treatment normalizes the rate of neurogenesis in stressed animals. (courtesy of Ronald Duman, Ph.D.)

duced in patients diagnosed with PTSD. Hippocampal volume was reduced in adults who were traumatized as adults (Bremner et al., 1995; Gurvits et al., 1996) or as children (Bremner et al., 1997; Stein et al., 1997). The reduction in hippocampal volume associated with PTSD is illustrated in Figure 2. These studies were conducted in populations where obvious confounding factors that might be common in prisoners of war or victims of torture, including head trauma and extreme nutritional deficiency, had been excluded. Further, the hippocampal volume reductions remained significant after adjusting statistically for the confounding effects of alcohol dependence and substance abuse. Although its importance has remained unclear, the fact of hippocampal volume reductions in PTSD soon became part of the accepted wisdom in PTSD research.

However, this field of research was recently perturbed by a series of interesting findings that called into question a simple model of stress–induced neurotoxicity. First, hippocampal reductions did not emerge over the initial six months following trauma (Bonne et al., 2001). This finding suggested that, when it occurred, hippocampal volume reductions did not fit a model of acute stress–induced neuronal injury. Second, hippocampal volume deficits were not observed in children with PTSD (De Bellis et al., 1999). This finding also supported the hypothesis that hippocampal deficits emerged as an interaction with neurodevelopmental processes. Third, a very creative study suggested that hippocampal volume deficits were a factor that predisposed to the development of PTSD following extreme stress rather than emerged as a consequence of stress exposure (Gilbertson et al., 2002). As indicated in Figure 3, these authors found that the hippocampal volume of non–traumatized monozygotic twins showed just as strong a negative correlation with the severity of PTSD of their traumatized twin as did the hippocampal volume of that traumatized twin. The interpretation of this study is complicated by relatively high rates of trauma in the co–twins of their PTSD sample, raising the

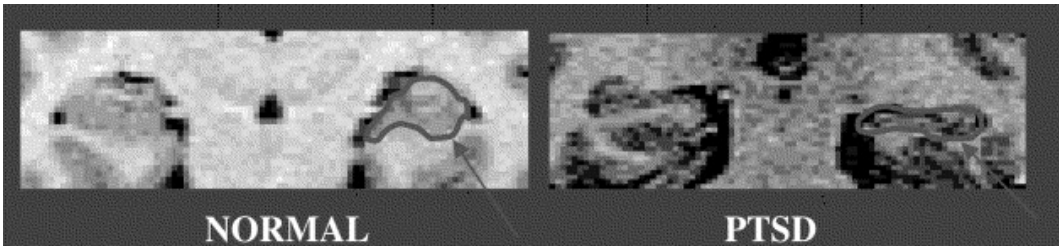

Figure 2.
MRI Images Containing the Hippocampus Illustrating Reduced Volume of This Structure in a Patient With PTSD Compared to the Volume of this Structure From a Healthy Comparison Subject. (Borrowed with permission from Elzinga and Bremner, 2002)

possibility that hippocampal volumes in this study reflect the interplay of vulnerability and traumatic response.

What is missing in the hippocampi of individuals with PTSD? Also, why are hippocampi smaller in PTSD patients? The answers to these questions are extremely important for understanding the epigenesis of PTSD, for understanding the neurobiology of resilience to stress exposure, and for understanding the adverse effects of stress on other disease processes. Reductions in hippocampal volume could reflect any or all of the pathological processes associated with stress exposure including excitotocity, atrophy, apoptosis, and disruption of neurogenesis. The pattern of these stress–related effects could parallel the findings in animals or might be unique to humans. However, if the reductions in hippocampal volume also reflect the predisposition to PTSD, then it may be impossible to predict the findings that would arise from postmortem research. Unexpected findings have emerged in both mood disorders and schizophrenia research. For example, postmortem studies conducted in tissue from patients with mood disorders reported reductions in glial populations (Ongur, Drevets, and Price, 1998; Rajkowska et al., 1999). Similarly, studies of gene expression in postmortem tissue from schizophrenic patients suggested that the processing of myelin might be abnormal (Hakak et al., 2001). The emerging technologies in cellular and molecular neuroscience are now being applied to human neuropathology (Lewis, 2002). As a result, the growing body of research utilizing postmortem human tissue has generated unexpected and important findings that now guide research into the pathophysiology and treatment of psychiatric illness.

Given the importance of studying postmortem tissue from individuals with PTSD, the absence of collections of brain tissue from individuals diagnosed with PTSD is a striking omission. A recent survey of brain banks from around the world yielded a total of 6 brains from individuals diagnosed with PTSD, of varying value to investigators due to the contexts of their collection and storage. Informal discussions with several investigators that conduct postmortem human brain research indicated that there was significant interest in expanding postmortem research into the field of PTSD if funding were available.

In the context of the war in Iraq and military actions in other parts of the world, it is now time to make the collection of brain tissue from individuals exposed to extreme stress a national research priority. The collection of brain tissue is a costly enterprise and it may need several sponsors. The urgency of this need is most immediate for the Department of Veterans Affairs where 25% of patients with mental health diagnoses carry the diagnosis of PTSD and 32% of all mental health costs are attributable to this diagnosis (from Department of Veterans Affairs, New England Program Evaluation Center). It should also be a high research priority for the Department of

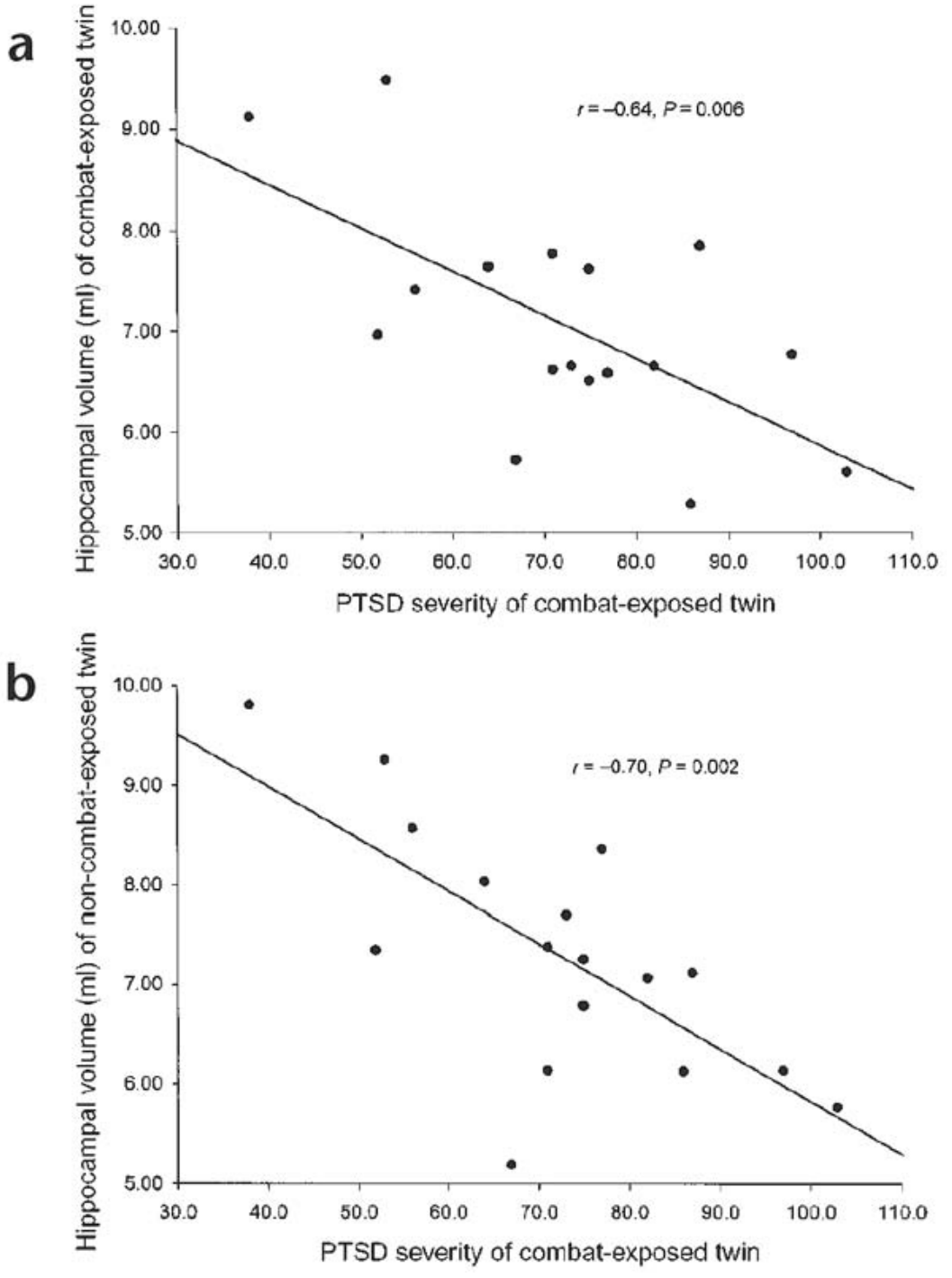

Figure 3.
Figure 3A illustrates that the volume of the hippocampus as assessed in MRI imaging shows a significant negative correlation with the severity of PTSD symptoms in patients with combat-related PTSD. Figure 3**B** illustrates that a similar negative correlation exists between the volume of the hippocampus in the non-combat-exposed twin and the severity of PTSD symptoms in the combat-exposed twin. (cited with permission from Gilbertson et al., 2002)

Defense, which would benefit by a better understanding of neurobiological factors related to resilience in the face of extreme stress. With respect to the National Institutes of Health (NIH), it would be fitting for the National Institute of Mental Health to support a brain bank initiative directed at PTSD and bioterrorism. Extreme stress exposure also contributes to other disease processes, including alcoholism, substance abuse, immunologic dysfunction, and geriatric memory impairment (Bremner and Narayan, 1998; Bremner et al., 1996; Dekaris et al., 1993; Kawamura, Kim, and Asukai, 2001; Ursano, 1997) that come under the purview of other NIH Institutes. Thus, research conducted using postmortem tissue from individuals exposed to extreme stress might reasonably draw support from multiple institutes.

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